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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/686,880	10/12/2000	Austin G. Smith	06999.0009	5994

22852 7590 09/13/2004

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 09/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/686,880	SMITH ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42,44-51,54,58 and 64-78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *42,44-51,54,58,64 and 65* is/are allowed.

6)☒ Claim(s) *66-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment filed 6-23-04 has been entered. Claims 42, 66 and 78 have been amended. Claims 42, 44-51, 54, 58 and 64-78 are pending and under consideration.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 66-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Smith et al., 2000 (US Patent 6,146,888) or Smith et al., 1994 (WO 94/24274) each in view of Anderson et al., 1997 (US Patent No. 5,654,183), Ericson et al., 1997 (Cell, Vol. 90, p. 169-180) and Xu et al., 1997 (The Journal of Biological Chemistry, Vol. 272, No. 6, pp. 3430-3436). Applicants' amendment filed 6-23-04 necessitates this new ground of rejection.

Claims 66-76 and 78 are directed to a method for generating a culture of purified or enriched neural progenitor cells comprising introducing into a pluripotent cell, such as ES cell, EG cell, or EC cell, a selectable marker, such as antibiotic resistance gene, that is differentially expressed in neural progenitor cells as compared to other cells, wherein the expression of the selectable marker is under the control of a promoter of a gene, such as Pax 3, Pax 6, Math-4a etc., that is differentially expressed in neural progenitor cells and the neural progenitor cells are selected according to differential expression of the selectable marker, wherein the pluripotent cell is cultured in vitro in the presence of a factor that induces differentiation of the cell into a neural progenitor cell. Claim 68 specifies genetically modifying pluripotent cells by deleting, substituting, or adding genes in said pluripotent cells. Claim 69 specifies using a second selectable marker for selection of neural progenitor cells. Claims 72-74 specify forming an embryoid body while culturing the pluripotent cells and/or dissociating differentiated cells to form a culture of individual cells. Claim 77 is directed to a method of preparing a neural progenitor cells or differentiated progeny for storage via freezing.

Smith ('888) teaches a method of enriching a population of mammalian stem cells, such as somatic stem cells and neural stem cells, by providing a mixed population of mammalian cells whose genome comprises at least one nucleic acid construct, for example, having a second nucleic acid construct encoding another antibiotic resistance gene, encoding an antibiotic resistance gene, such as neo gene, operatively linked to a promoter, such as Oct4 promoter, preferentially expressed said antibiotic gene in mammalian stem cells, and selecting the mammalian stem cells in the presence of antibiotic, such as G418 (e.g. column 12-14). Smith also teaches forming embryoid bodies from ES cells and selecting undifferentiated mammalian

stem cells in the presence of G418 (e.g. column 9-10). Smith further teaches "a method of isolating and/or enriching and/or selectively propagating animal stem cells, genetically modified animal cells and animal for use in said method, transgenic animals providing a source of such cells" (e.g. column 1, first paragraph).

Smith (WO 94/24274) teaches a method of isolating and/or enriching propagating animal or mammalian stem cells, such as somatic stem cells and neural stem cells, by providing cells containing a selectable marker encoding an antibiotic resistance gene, such as neo gene, operatively linked to a promoter, such as Oct4 promoter, differentially expressed said antibiotic gene in desired stem cells and cells other than stem cells, whereby differential expression of said selectable marker results in preferential isolation and/or survival of the desired stem cells, and cells contain two selectable markers also can be used for this method (e.g. abstract, p. 2, 3, 22, 23). Smith also teaches forming embryoid bodies from ES cells and selecting undifferentiated mammalian stem cells in the presence of G418 (e.g. p. 15-17). Smith further teaches "a method of isolating and/or enriching and/or selectively propagating animal stem cells, genetically modified animal cells and animal for use in said method, transgenic animals providing a source of such cells" (e.g. p. 1, first paragraph).

Smith does not teach culturing the pluripotent cell in vitro in the presence of a factor that induces differentiation of the cell into a neural progenitor cell, using promoter of a gene that is differentially expressed in neural progenitor cells for the selection of neural progenitor cells and storage of said cells via freezing.

Anderson teaches a method for obtaining a cellular composition comprising one or more cells having at least one property characteristic of a glial or neural progenitor cell or a

multipotent stem cell precursor of such cells by preparing a cell suspension comprising a population of cells from a mammalian tissue, such as an embryo, contacting the cell suspension with a culture medium and substrate allowing generation and self-renewal of the glial or neural progenitor cells in a feeder-cell independent culture (e.g. bridging column 3-4). In the feeder-cell independent culture, the feeder cells provide a substratum for the attachment of the cells from the tissue of interest and also serve as a source of mitogen and survival factors, which are provided by supplementation of the liquid culture medium with either purified factors or crude extracts from other cells or tissues (e.g. column 8). Chick embryo extract (CEE) is added to plating medium (complete medium) which allows the propagation of undifferentiated neural crest cells and clonal propagation of neurons and immature glia cells. CEE is also added to differentiation medium for the differentiation of neuronal cells and production of schwann cells (e.g. Figure 3, Examples 1, 2 and 3).

Ericson teaches "Pax 6 establishes distinct ventral progenitor cell populations and controls the identity of motor neurons and ventral interneurons, mediating graded Shh signaling in the ventral spinal cord and hindbrain (e.g. abstract). Pax 6 is expressed by undifferentiated cells in the ventral region of the neural tube (e.g. p. 169, right column). Therefore, Pax 6 is a neural progenitor cell-specific gene.

Xu reports that Pax 6 is a homeobox gene and is expressed in a spatially and temporally restricted pattern during early embryogenesis. Pax 6 promoter has a TATA like-box at –26 bp and two CCAAT boxes at –70 and –100 bp. Xu identified a 96 bp region that is required for basal Pax 6 promoter activity (e.g. abstract).

It would have been obvious for one of ordinary skill in the art at the time of the invention to operably link Pax 6 gene promoter as taught by Xu to at least a selectable marker encoding an antibiotic resistance gene, such as neo gene, for enriching mammalian stem cells, such as neural stem cells, as taught by Smith ('888 or WO 94/24274) because Ericson shows that Pax 6 gene is a neural progenitor cell-specific gene and Smith teaches a method of enriching a population of mammalian stem cells, such as neural stem cells, by using at least one nucleic acid construct encoding an antibiotic resistance gene, such as neo gene, operatively linked to a promoter preferentially expressed said antibiotic gene in mammalian stem cells. It also would have been obvious for one of ordinary skill in the art to store the enriched neural progentiro cells by freezing since it was well known in the art to freeze the cells with cryoprotectant, such as DMSO. Further, it would have been obvious for one of ordinary skill in the art at the time of the invention to induce differentiation of a neural crest stem cell into a neural progenitor cell by using a medium containing CEE as taught by Anderson while generating a culture that is purified or enriched in neural progenitor cells because Anderson teaches adding CEE in the medium for preparing neural crest stem cells and neural progenitor cells.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to isolate or enrich the mammalian stem cells, such as neural stem cells, or genetically modified animal cells and transgenic animals providing a source of such cells as taught by Smith or in order to obtain a cellular composition comprising one or more cells having at least one property characteristic of a glial or neural progenitor cell or a multipotent stem cell precursor of such cells as taught by Anderson with reasonable expectation of success.

4. Claims 66-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al., 2000 (US Patent 6,146,888) or Smith et al., 1994 (WO 94/24274) each in view of Anderson et al., 1997 (US Patent No. 5,654,183) and Gradwohl et al., 1996 (Developmental Biology, Vol. 180, p. 227-241). Applicants' amendment filed 6-23-04 necessitates this new ground of rejection.

Claims 66-76 and 78 are directed to a method for generating a culture of purified or enriched neural progenitor cells comprising introducing into a pluripotent cell, such as ES cell, EG cell, or EC cell, a selectable marker, such as antibiotic resistance gene, that is differentially expressed in neural progenitor cells as compared to other cells, wherein the expression of the selectable marker is under the control of a promoter of a gene, such as Pax 3, Pax 6, Math-4a etc., that is differentially expressed in neural progenitor cells and the neural progenitor cells are selected according to differential expression of the selectable marker, wherein the pluripotent cell is cultured in vitro in the presence of a factor that induces differentiation of the cell into a neural progenitor cell. Claim 68 specifies genetically modifying pluripotent cells by deleting, substituting, or adding genes in said pluripotent cells. Claim 69 specifies using a second selectable marker for selection of neural progenitor cells. Claims 72-74 specify forming an embryoid body while culturing the pluripotent cells and/or dissociating differentiated cells to form a culture of individual cells. Claim 77 is directed to a method of preparing a neural progenitor cells or differentiated progeny for storage via freezing.

Smith teaches a method of enriching a population of mammalian stem cells, such as somatic stem cells and neural stem cells, by providing a mixed population of mammalian cells whose genome comprises at least one nucleic acid construct, for example, having a second

nucleic acid construct encoding another antibiotic resistance gene, encoding an antibiotic resistance gene, such as neo gene, operatively linked to a promoter, such as Oct4 promoter, preferentially expressed said antibiotic gene in mammalian stem cells, and selecting the mammalian stem cells in the presence of antibiotic, such as G418 (e.g. column 12-14). Smith also teaches forming embryoid bodies from ES cells and selecting undifferentiated mammalian stem cells in the presence of G418 (e.g. column 9-10). Smith further teaches "a method of isolating and/or enriching and/or selectively propagating animal stem cells, genetically modified animal cells and animal for use in said method, transgenic animals providing a source of such cells" (e.g. column 1, first paragraph).

Smith (WO 94/24274) teaches a method of isolating and/or enriching propagating animal or mammalian stem cells, such as somatic stem cells and neural stem cells, by providing cells containing a selectable marker encoding an antibiotic resistance gene, such as neo gene, operatively linked to a promoter, such as Oct4 promoter, differentially expressed said antibiotic gene in desired stem cells and cells other than stem cells, whereby differential expression of said selectable marker results in preferential isolation and/or survival of the desired stem cells, and cells contain two selectable markers also can be used for this method (e.g. abstract, p. 2, 3, 22, 23). Smith also teaches forming embryoid bodies from ES cells and selecting undifferentiated mammalian stem cells in the presence of G418 (e.g. p. 15-17). Smith further teaches "a method of isolating and/or enriching and/or selectively propagating animal stem cells, genetically modified animal cells and animal for use in said method, transgenic animals providing a source of such cells" (e.g. p. 1, first paragraph).

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Anderson teaches a method for obtaining a cellular composition comprising one or more cells having at least one property characteristic of a glial or neural progenitor cell or a multipotent stem cell precursor of such cells by preparing a cell suspension comprising a population of cells from a mammalian tissue, such as an embryo, contacting the cell suspension with a culture medium and substrate allowing generation and self-renewal of the glial or neural progenitor cells in a feeder-cell independent culture (e.g. bridging column 3-4). In the feeder-cell independent culture, the feeder cells provide a substratum for the attachment of the cells from the tissue of interest and also serve as a source of mitogen and survival factors, which are provided by supplementation of the liquid culture medium with either purified factors or crude extracts from other cells or tissues (e.g. column 8). Chick embryo extract (CEE) is added to plating medium (complete medium) which allows the propagation of undifferentiated neural crest cells and clonal propagation of neurons and immature glia cells. CEE is also added to differentiation medium for the differentiation of neuronal cells and production of schwann cells (e.g. Figure 3, Examples 1, 2 and 3).

Gradwohl discloses a cDNA sequence, including 5' untranslated sequence, encoding a bHLH Math4A protein and reports that Math4A expression is restricted to undifferentiated neural precursors. Gradwohl suggests that Math4A may regulate early neural development by

functioning with ubiquitous bHLH proteins or being associated with other neural-specific bHLH proteins (e.g. abstract).

It would have been obvious for one of ordinary skill in the art at the time of the invention to operably link Math4A 5' untranslated sequence as taught by Gradwohl to at least a selectable marker encoding an antibiotic resistance gene, such as neo gene, for enriching mammalian stem cells, such as neural stem cells, as taught by Smith ('888 or WO 94/24274) because Gradwohl shows that Math4A gene is a neural precursor cell-specific gene and Smith teaches a method of enriching a population of mammalian stem cells, such as neural stem cells, by using at least one nucleic acid construct encoding an antibiotic resistance gene, such as neo gene, operatively linked to a promoter preferentially expressed said antibiotic gene in mammalian stem cells. It also would have been obvious for one of ordinary skill in the art to store the enriched neural progentiro cells by freezing since it was well known in the art to freeze the cells with cryoprotectant, such as DMSO. Further, it would have been obvious for one of ordinary skill in the art at the time of the invention to induce differentiation of a neural crest stem cell into a neural progenitor cell by using a medium containing CEE as taught by Anderson while generating a culture that is purified or enriched in neural progenitor cells because Anderson teaches adding CEE in the medium for preparing neural crest stem cells and neural progenitor cells.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to isolate or enrich the mammalian stem cells, such as neural stem cells, or genetically modified animal cells and transgenic animals providing a source of such cells as taught by Smith or in order to obtain a cellular composition comprising one or more cells

having at least one property characteristic of a glial or neural progenitor cell or a multipotent stem cell precursor of such cells as taught by Anderson with reasonable expectation of success.

Conclusion

Claims 66-78 are rejected. Claims 42, 44-51, 54, 58, 64 and 65 are in condition for allowance.

5. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for this group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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Shin-Lin Chen, Ph.D.